Delayed graft function and the risk of acute rejection in the modern era of kidney transplantation

W. Kelly Wu[1], Olusegun Famure[1,2], Yanhong Li[1] and S. Joseph Kim[1,2,3,4]

[1]Multi-Organ Transplant Program, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada; [2]Division of Nephrology and the Kidney Transplant Program, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada; [3]Division of Nephrology and the Renal Transplant Program, St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada and [4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

Delayed graft function (DGF) is commonly considered a risk factor for acute rejection, although this finding has not been uniformly observed across all studies. The link between DGF and acute rejection may have changed over time due to advances in immunosuppression and medical management. Here we conducted a cohort study of 645 patients over 12 years to evaluate the association of DGF and biopsy-proven acute rejection (BPAR) in a modern cohort of kidney transplant recipients. DGF was defined as the need for at least one dialysis session in the first week after kidney transplantation. The 1-, 3-, and 5-year cumulative probabilities of BPAR were 16.0, 21.8, and 22.6% in the DGF group, significantly different from the 10.1, 12.4, and 15.7% in the non-DGF group. In multivariable Cox proportional hazards model, the adjusted relative hazard for BPAR in DGF (vs. no DGF) was 1.55 (95% confidence interval (CI): 1.03, 2.32). This association was generally robust to different definitions of DGF. The relative hazard was also similarly elevated for T-cell- or antibody-mediated BPAR (1.52 (0.92, 2.51) and 1.54 (0.85, 2.77), respectively). Finally, the association was consistent across clinically relevant subgroups. Thus DGF remains an important risk factor for BPAR in a contemporary cohort of kidney transplant recipients. Interventions to reduce the risk of DGF and/or its aftereffects remain of paramount importance to improve kidney transplant outcomes.

Kidney International advance online publication, 24 June 2015; doi:10.1038/ki.2015.190

KEYWORDS: acute rejection; delayed graft function; kidney transplantation

Correspondence: *S. Joseph Kim, Division of Nephrology and the Kidney Transplant Program, Toronto General Hospital, University Health Network, University of Toronto, 585 University Avenue, 11-PMB-129, Toronto, Ontario M5G 2N2, Canada. E-mail: joseph.kim@uhn.ca*

Received 18 October 2014; revised 9 April 2015; accepted 23 April 2015

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD). Despite its benefits, recipients may experience posttransplant complications that can negatively impact long-term allograft and patient outcomes. Delayed graft function (DGF) is a common complication experienced by kidney transplant recipients, particularly among those receiving deceased donor kidneys. It is most often defined as the need for dialysis within the first 7 days after kidney transplantation. The incidence of DGF ranges from 20% to 50% in deceased and from 4% to 10% in living donor kidney transplant recipients, with variations in incidence due to recipient, donor, and transplant factors, as well as the DGF definition used.

DGF has been associated with poor clinical outcomes, including death with graft function and graft failure.[1,2] DGF may also contribute to the development of chronic graft dysfunction, which may ultimately compromise graft longevity.[3] An increased tendency to chronic graft failure may be mediated by a history of acute rejection in patients with DGF. The ischemia–reperfusion injury leading to DGF may also increase the expression of human leukocyte antigen molecules on endothelial cell surfaces and thus increase the immunogenicity of the allograft.[3] Deciphering the links between DGF, acute rejection, and long-term outcomes may be of value in developing strategies to minimize chronic allograft dysfunction and graft failure.

Although some past studies have found no significant increase in the risk of acute rejection associated with DGF,[4,5] other reports have observed a direct relationship between the two entities.[2] However, most of these studies were conducted in cohorts from the 1990s, and a recent, more comprehensive assessment of this relationship is lacking. New immunosuppressive strategies aimed at decreasing the incidence of acute rejection have been developed and implemented in the past decade.[6] Wider use of expanded criteria donors (ECDs) and donation after circulatory death (DCD) has further increased the incidence of DGF, but the associated risk and outcome of acute rejection in patients receiving these kidneys are not clear. Furthermore, the validity of the traditional DGF definition has been questioned,[7] and thus alternate definitions have been considered.[8,9] The purpose of this study is to

evaluate and quantify the association of DGF and biopsy-proven acute rejection (BPAR) in the current era of deceased donor kidney transplantation at a large Canadian kidney transplant center and to determine whether the association is sensitive to the definition of DGF used.

RESULTS

After applying the *a priori* exclusion criteria, 645 deceased donor kidney transplant recipients were included in the final study cohort (Figure 1). A total of 233 (36.1%) experienced DGF. During 2744.6 patient-years of follow-up (median follow-up 3.5 years), there were 111 BPAR events. During 3164.1 patient-years of follow-up (median follow-up 4.5 years), there were 57 graft losses and 62 deaths with graft function resulting in 119 total graft failure events. The proportion of missing data across all the data elements used in this analysis ranged from 0% to 24% (Supplementary Appendix, SA-1 online).

Baseline characteristics for the DGF and non-DGF groups are shown in Table 1. Recipients who developed DGF had greater body mass index, higher prevalence of diabetes as the cause of ESRD, and longer time on pretransplant dialysis. Recipients with DGF were also more likely to receive kidneys from donors who were older, male, and recovered after circulatory death. Other characteristics were similar between DGF and non-DGF groups. In particular, there were no significant differences in cold ischemic time, human leukocyte antigen mismatches, and transplant era. Notably, the distribution of calcineurin inhibitor levels over the first year posttransplant showed considerable overlap in DGF and non-DGF patients (Supplementary Appendix, SA-2 online).

The cumulative probabilities of developing BPAR in DGF and non-DGF groups are displayed in Figure 2. The cumulative probability was greater in DGF patients at all points over the follow-up period. The 1-, 3-, and 5-year probabilities of BPAR were 16.0% (95% confidence interval (CI): 11.8, 21.3), 21.8% (95% CI: 16.8, 27.9), and 22.6% (95% CI: 17.5, 28.9) in the DGF group and 10.1% (95% CI: 7.6, 13.5), 12.4% (95% CI: 9.5, 16.1), and 15.7% (95% CI: 12.2, 20.1) in the non-DGF group, respectively (log-rank $P=0.01$).

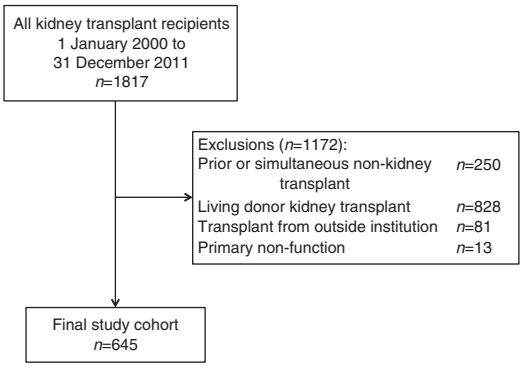

Figure 1 | Study flow diagram.

Table 2 shows the relative hazards for BPAR in DGF versus non-DGF patients estimated from multivariable Cox proportional hazards models. DGF was associated with an unadjusted hazard ratio of 1.66 (95% CI: 1.14, 2.42) for BPAR over the follow-up period. Sequential adjustments for an expanding set of covariates did not appreciably alter the univariable association. In the fully adjusted model (Model 4), the hazard ratio for BPAR was 1.55 (95% CI: 1.03, 2.32) in patients experiencing DGF vs. no DGF. Similar findings were seen when a backward stepwise procedure was used for covariate selection (Model 5). Moreover, the results were robust to whether graft failure or death with graft function was treated as censoring or competing events (Supplementary Appendix, SA-3 and SA-4 online).

The robustness of the DGF-BPAR association was evaluated as a function of the DGF definition used in the analysis (Table 3). The majority of the definitions evaluated showed a similarly elevated relative hazard for BPAR in patients who developed DGF in the postoperative setting. Interestingly, definitions that incorporated measures of kidney function in conjunction with the need for dialysis (definitions 5 and 6) generally showed a more attenuated association.

Figure 3 shows the Kaplan–Meier curves for the cumulative probability of developing acute antibody-mediated rejection (ABMR) and T-cell-mediated rejection (TCMR). DGF patients showed a higher cumulative probability of developing both types of BPAR over follow-up. However, the absolute risk of TCMR was greater than that of ABMR in both the DGF and non-DGF groups. The risk of developing ABMR increased most rapidly during the first month after transplant, whereas the risk of TCMR appeared to persist for a longer duration. In Cox proportional hazards models, the adjusted hazard ratios for acute TCMR and ABMR were 1.52 (95% CI: 0.92, 2.51; $P=0.10$) and 1.54 (95% CI: 0.85, 2.77; $P=0.15$), respectively. Similar results were observed for all DGF definitions examined (data not shown).

An evaluation of potential subgroup effects is depicted as a forest plot in Figure 4. Notably, the point estimates showed that recipients who were older, diabetic, unsensitized, and received ECD kidneys at the time of transplantation tended to exhibit a more diminished association between DGF and BPAR. Interestingly, DCD kidney recipients showed a more accentuated hazard ratio than non-DCD kidney recipients. However, there was no statistically significant effect measure modification observed across any subgroups studied (P-value for interaction ≥ 0.13).

DISCUSSION

This study confirms that DGF continues to be an important risk factor for BPAR in the modern era of deceased donor kidney transplantation. The multivariable adjusted relative hazard for BPAR was significantly elevated at 1.64-fold in patients experiencing DGF (vs. no DGF), which is consistent with the findings of the meta-analysis by Yarlagadda *et al.*[2] The association was generally persistent across different